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News and Views

Build-up of esterified aminolevulinic-acid-derivative-induced porphyrin fluorescence in normal mouse skin

Qian Peng [a,b], Johan Moan [b], Trond Warloe [c], Vladimir Iani [b], Harald B. Steen [b], Alf Bjørseth [d], Jahn M. Nesland [a]

[a] Department of Pathology, Institute for Cancer Research, The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway
[b] Department of Biophysics, Institute for Cancer Research, The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway
[c] Department of Surgical Oncology, The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway
[d] Research Foundation, The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway

During the past 5 years, aminolevulinic-acid(ALA)-mediated photodynamic therapy (PDT) of cancer is one of the most rapidly developing fields in PDT research. Since Kennedy et al. [1] proposed the use of topically ALA-based PDT of cutaneous diseases in 1990, much interest has arisen in many laboratories [2–4]. In particular, promising clinical results have been obtained in the treatment of superficial basal cell carcinoma [5,6]. However, this modality is not optimally effective to sensitize the nodular lesions to complete destruction, probably owing to the limited skin penetration of ALA and production of ALA-induced porphyrins in the deep layers of the lesions [7]. Thus enhancement of both ALA absorption and ALA-derived porphyrin production in the nodular lesions is a crucial factor to improve the technique. Recently we have studied the effects of methylester, ethylester and propylester derivatives of ALA (H_2N–CH_2COCH_2–CH_2COO–R; R can be CH_3, CH_2–CH_3 or CH_2–CH_2–CH_3) on production of porphyrins in the normal skin of female Balb/c athymic nude mice. We found, by means of an optical-fiber-based point monitoring system in situ, that a slight porphyrin fluorescence was built up already 1 h after topical application of the derivatives (20% in a cream) in the right flank of the mice. The maximum fluorescence intensity was found 14 h after the application for both free ALA and its ester derivatives, but the porphyrin fluorescence induced by the ALA esters in the skin was stronger than that induced by free ALA (Fig. 1). Moreover, as can be seen in Fig. 2, 14 h after the topical application no fluorescence of ALA-ester-induced porphyrins was detected in other areas than that in which the cream was applied (ear, liver, muscle and brain). However, in the case of free ALA, a significant fluorescence was seen in the skin outside the area of application. Fluorescence imaging of the skin treated with the three derivatives showed fluorescence of the ester derivative-induced porphyrins in the epidermis, epithelial hair follicles and sebaceous glands. In the case of intraperitoneal (i.p.) injection (150 mg

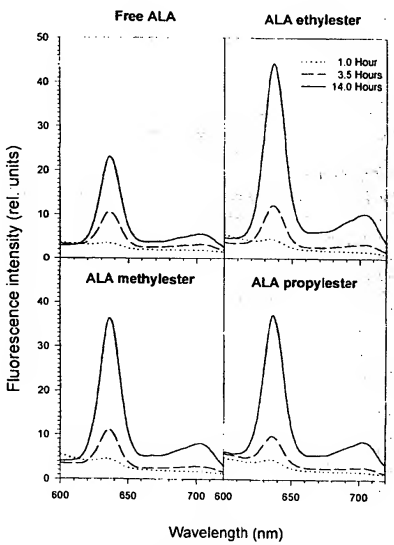

Fig. 1. Fluorescence spectra of free ALA- and its three ester derivative-induced porphyrins in the normal mouse skin in situ at various time intervals (as indicated) after topical application.

kg^{-1}) the fluorescence of the ALA methylester-induced porphyrins in the skin was built up 15 min after injection. The peak value was found at around 1–2 h and disappeared within 12 h post injection. This kinetic pattern was similar to that of the fluorescence of free ALA-induced porphyrins in the skin

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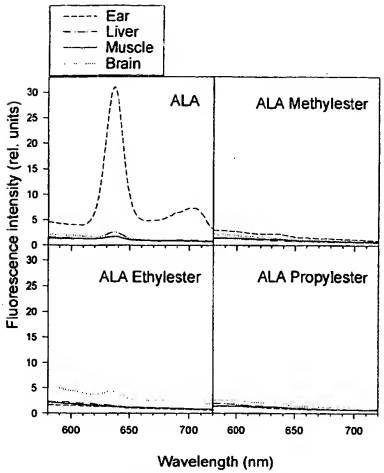

Fig. 2. Fluorescence spectra of free ALA- and its three ester derivative-induced porphyrins in the ear, liver, muscle and brain of the mice 14 h after topical application.

following i.p. injection of the same dose, although the fluorescence decreased more rapidly in the case of the ester than in the case of free ALA. The present data indicate that all derivatives studied were taken up, de-esterified and finally converted into porphyrins in the epidermis, epithelial hair follicles and sebaceous glands of the nude mice with a higher porphyrin production than that of free ALA. This is in agreement with our preliminary results obtained in a study of human nodular basal cell carcinoma that demonstrated that th fluorescence of the ALA ester-induced porphyrins was built up more rapidly with a higher intensity and a more homogenous distribution than those of free ALA-induced porphyrins in the lesi ns [8]. Interestingly, a strong fluorescence of free ALA-induced porphyrins was found in regions of the skin outside the area where the cream was topically applied. This indicates that, after topical application, free ALA is transported in the blood and porphyrins may subsequently be formed in all organs containing the enzymes of the heme synthesis pathway or ALA-induced porphyrins are initially formed in the liver and then transported to other tissues via blood circulation. This may lead to skin photosensitivity in areas where free ALA is even not topically applied. However, none of the ester derivatives studied induced porphyrin fluorescence at distant skin sites.

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